II. REMARKS

I. Claims in the Case

Claims 16-18 are canceled and new claim 31 has been added. Claims 1-15 and 19-31 are pending, of which claims 2, 11, 13, 14, 19, 21-24, 27 and 28 are withdrawn, subject to rejoinder, and claim 1 is amended. Claims 1, 3-10, 12, 15, 20, 25, 26, 29 and 30-31 are pending and under examination.

II. Election/Restriction

Applicants note the Examiner's comments regarding election/restriction and believe that no responsive comments are called for.

III. Claim Objections

The Action next objects to the claims to the extent they read on non-elected inventions. Applicants respectfully traverse.

In response, Applicants note that all of the claims that read *only* on non-elected inventions have been withdrawn, subject to rejoinder. To the extent the remaining claims read on a non-elected invention, such claims should be considered linking claims which claims are not subject to withdrawal. See MPEP 809 ("The linking claims must be examined with, and thus are considered part of, the invention elected.") Thus, maintaining the linking claims in the case is appropriate.

IV. Obviousness Rejections

Lastly, all of the claims have been rejected as obvious over the combination of Roth *et al.* ("Roth I") in view of Roth *et al* ("Roth II") further in view of Staar *et al.* ("Staar"). Applicants respectfully traverse.

Firstly we would note that the present invention is concerned with the treatment of recurrent cancer and is based on the surprising finding that when recurrent cancer patients in p53

gene therapy trials (typically cancers that had become resistant to conventional treatment) were treated with p53 gene therapy, the p53 gene therapy somehow rendered the recurrent cancer once again highly amenable to conventional therapy at a future time when the therapeutic gene was no longer being expressed in the tumor . Indeed, very surprising increases in survival relative to historical and treatment controls were seen in these patients. While the underlying mechanisms are unknown, it may be speculated that the p53 therapy somehow reconditioned or reprogrammed the apoptotic pathways of the tumor to make it once again amenable to conventional therapy or the p53 treatment induced apoptosis in subpopulations of tumor cells most resistant to treatment with subsequent outgrowth of tumor cell populations more sensitive to standard therapies. These potential mechanisms are not mutually exclusive and other mechanisms may have contributed to the unexpected findings.

The foregoing observation is entirely distinct from what is described in Roth I – Roth I involves essentially concurrent, combination therapy with p53 and DNA damaging agents, and is based on the finding that essentially co-administration of p53 and DNA damaging agents results in a synergistic or greater than additive apoptotic effect. While Roth I teaches that the co-administration does not have to be at *precisely* the same time (and their order of administration can be reversed), it does stress the importance of administering within 24 hours of each other in order to achieve the synergistic apoptotic effect:

> Naturally, it is also envisioned that the target cell may be first exposed to the DNA damaging agent(s) and then contacted with a p53 protein or gene, or vice versa. However, in embodiments where the DNA damaging factor and p53 are applied separately to the cell, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell. ***In such instances, it is contemplated that one would contact the cell with both agents within about 12-24 hours of each other, and more preferably within about 6-12 hours of each other, with a delay time of only about 12 hours being most preferred.***

Roth I, col. 4, lines 27-39 (emphasis ours). From the foregoing it is evident that Roth I teaches that the DNA damaging agent and the p53 gene therapy should be administered within 24 hours of each other, thus teaching away from the present invention. Moreover, Roth I only mentions recurrent cancer in passing and says nothing about treatment regimens that have special efficacy in the case of recurrent disease.

Roth II is similarly irrelevant. Roth II does indicate that patients with recurrent disease were treated with p53 therapy. However, the Action fails to point us to any teaching in Roth II regarding to the effect that such p53 therapy will have promote a longer survival upon further conventional treatment subsequent to the p53 therapy.

We also fail to see the relevancy of Staar, which simply sets forth a conventional chemotherapy regimen, but says nothing about administering conventional therapy following p53 gene therapy in order to dramatically improve survival.

We would note that various claim amendments to claim 1, and new claim 31, have been entered in an attempt to further distance the claimed subject matter from the cited art. For example, both claims now require at least 7 days post-p53 therapy before administration. While it is believed that advantages in accordance with the invention could well be realized with a shorter interval, the amendment here is made for now to distance the present invention from the very different invention of Roth I. Further, we have attempted to craft both main claims to clarify that it is contemplated that the post-p53 conventional therapy is not administered until at the time frame set forth in the claim when the p53 transgene is no longer expressed (*i.e.*, at least 7 days, in the case of claims 1 and 31, and about 14 days in the case of claim 20).

Lastly, the Action's reliance on the "optimization of ranges" doctrine is totally misplaced here. As specifically pointed out in MPEP 2144.05, II, B, the "optimization of ranges" doctrine is

only relevant to a recognized "result-effective variable", that is, optimization of an already recognized relationship:

> B. Only Result-Effective Variables Can Be Optimized
>
> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result- effective variable.). See also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

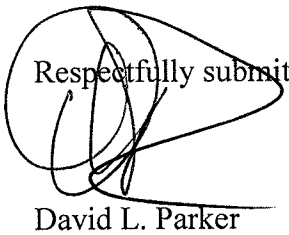
MPEP 2144.05, II. B. Here, the surprising finding that post-gene therapy administration conventional therapy in recurrent cancer can greatly improve survival is totally a novel observation and can in no way be said to constitutes a "result-effective variable" As such, our situation is not unlike that in *In re Antonie*, mentioned in the above MPEP excerpt, where the court observed that the prior art failed to recognize the relationship between treatment capacity as a function of tank volume to contractor ratio, in holding that the optimization doctrine did not apply.

We believe that by the foregoing arguments, it can now be seen that the claimed subject matter is both novel and non-obvious and it is requested that the Examiner reconsider and withdraw the rejection of the claims.

V. Conclusion

It is believed that the present response is a complete response to the outstanding office action. The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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